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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,811	06/29/2001	Thomas D. Madden	16303-008020	7024

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EXAMINER
OSTRUP, CLINTON T

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/22/2002 5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,811	MADDEN ET AL.	
	Examiner	Art Unit	
	Clinton Ostrup	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-25 are pending in this application.

Priority

Priority to U.S. Provisional Application Numbers 60/264,616, filed January 29, 2001, and 60/215,556 filed June 30, 2000 has been acknowledged. There is a discrepancy between the date in which applicant is claiming priority to U.S. Provisional Application Number 60/264,616. Specifically the Office's records indicate this application was filed January 29, 2001, whereas applicant claims priority to this application as being filed on January 25, 2001 (See: Application Data Sheet) and on January 26, 2001 (See: page 1, paragraph 1 of specification). Correction of the priority date is required.

Specification

The disclosure is objected to because of the following informalities: page 1, line 5 does not state a U.S. Patent Application No. Appropriate correction is required.

Claim Objections

Claims 1-2, 10-11, 16, 21, and 23-24 objected to because of the following informalities: The usage of parenthesis in these claims is informal and the claims should be amended to eliminate such informalities. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 32-35, 37, 39-57, and 60-63 of copending Application No. 09/896,812. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to liposomal formulations comprising camptothecin and/or topotecan compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 24-25 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 12, and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phraseology "trace amounts or greater" in claims 9 and 12, is a relative phrase which renders the claim indefinite. The phrase " trace amounts or greater " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of this claim are unascertainable because it is unclear what the lower limit of "trace amounts or greater" includes or excludes.

Claims 24-25 provide for the use of topotecan in the manufacture of a medicament, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater et al., 6,355,268 and further in view of NEXSTAR PHARMACEUTICALS, INC., WO 99/13816 (NEXSTAR).

Slater et al., disclose liposome-entrapped topoisomerase inhibitors including camptothecin and camptothecin analogs such as topotecan and irinotecan. See: col. 1, lines 42-52, col. 2, line 65 – col. 3, line 15. The reference teaches that the liposome formulations remain in the blood stream for prolonged periods of time and retains the drugs antitumor activity. See: col. 2, lines 37-43 and abstract. The primary reference teaches vesicle forming lipids in an amount between about 1-20 mole percent and having entrapped within the liposome a topoisomerase I/II inhibitor at a concentration of about 0.10-0.20 µmole drug per µmole lipid. See: col. 2, lines 45-64.

Slater et al., teach the vesicle-forming lipid as hydrogenated soy phosphatidylcholine, distearoyl phosphatidylcholine or sphingomyelin and other suitable lipids, including glycolipids and sterols such as cholesterol, can be used as vesicle forming lipids. See: col. 3, lines 30-68. The reference teaches that the effective amount

of the topoisomerase can vary depending on factors known to those skilled in the art and one skilled in the art would be able to consider such factors and make a determination regarding the effective amount. See: col. 5, lines 34-64.

The primary reference teaches that encapsulation of camptothecin and its analogs, which have a α-hydroxy lactone ring which hydrolyzes in aqueous environments, is stabilized by entrapping these compounds in a liposome. Furthermore, Slater et al., specifically teach that the prior art has shown that a liposome-entrapped formulation of topotecan is stabilized and hydrolysis of the lactone ring is inactivated. See: col. 1, line 53 – col. 2, line 23. The primary reference also teaches that a gradient can be produced by including a selected ionophore in the liposomes and that said ionophore creates a lower inside/higher outside pH gradient. See: col.10, line 50 –col. 11, line 5.

The primary reference teaches liposome-entrapped topotecan as being administered to animals as an intravenous bolus injection and the liposome-entrapped topotecan formulation as decreasing tumor volume and in some instances, complete remission of tumor mass. See: col. 16, line 49 – col. 18, line 33. The reference describes how the liposome-entrapped topotecan has a significantly longer circulation time that the free form of the drug. Figures 4A and 4B show lipo-topotecan as remaining in the blood plasma in detectible concentrations for up to 72 hours post administration as compared to free topotecan remaining in the blood plasma in detectible concentrations for only about 2 hours post administration. See: col. 23, line 6 – col. 24, line 30.

Although the primary reference teaches liposome-encapsulated camptothecin and its analogs, including topotecan, and said liposomes as being administered as an intravenous bolus injection for reducing tumor size, the primary reference does not specifically teach the dosage of instant claims 1, 5, 17, and 22-23, the ratio of sphingomyelin to cholesterol of instant claim 4, and the methods of treatment of instant claims 18-21.

While the reference is silent with respect to the specific dosage as claimed instantly in claims 1, 5, 17, and 22-23, differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.

In the instant case, the primary reference teaches that the skilled artisan would readily recognize that the effective amount of the topoisomerase can vary depending on factors known to those skilled in the art and one skilled in the art would be able to consider such factors and make a determination regarding the effective amount. Therefore, the specific amounts of instant 1, 5, 17, and 22-23 would have been obvious to and easily determined by one having ordinary skill in the art at the time the invention was made, because the skilled artisan would have to find an effective amount based upon factors known to the skilled artisan.

NEXSTAR discloses liposomal camptothecin formulations having improved pharmacokinetics, enhanced efficacy as anti-tumor agents. See: abstract. The

secondary reference teaches that cholesterol is known to improve liposomal stability and prevent loss of phospholipid to lipoproteins in vivo. See: page 11, line 21 – page 12, line 12. The secondary reference teaches phospholipid to cholesterol ratios, which overlap those of instant claim 4. Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to add cholesterol as taught by both the primary and secondary references in amounts taught by the secondary reference because of the expectation of obtaining a liposomal formulation with improved stability and which prevents phospholipid loss to lipoproteins in vivo.

NEXSTAR teaches the that the growth of tumors associated with all cancers is contemplated by their invention and specifically teach lung cancer, colorectal cancer, breast cancer, thus meeting the specific methods of treatment as claimed instantly in claims 18-21. See: page 16, line 7-16. It would have been obvious to one having ordinary skill in the art at the time the invention was made to have used liposome-encapsulated camptothecin and camptothecin analogs such as topotecan as taught by Slater et al., to treat the various cancers as taught by NEXSTAR because of the expectation that encapsulated-encapsulated camptothecin and camptothecin analogs such as topotecan would have similar topoisomerase inhibition activities on different types of cell lines and therefore, have tumor suppression activities on different types of cancers.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on M-F (8:30am-5:00pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup

Examiner

Art Unit 1619

July 18, 2002

FREDERICK KRASS
PRIMARY EXAMINER
GROUP 1600